BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 40, NO. 9 SEPTEMBER, 1964

THE FDA AND THE PREVENTION OF DRUG EMBRYOPATHY*

MATTHEW J. ELLENHORN

Chief, New Drug Surveillance Branch
Division of New Drugs, Bureau of Medicine, Food and Drug Administration
U. S. Department of Health, Education, and Welfare

I have been designated this evening to discuss the role of the Food and Drug Administration in preventing the repetition, at least in the United States, of another thalidomide-type episode. In order to understand the function and evolution of the Food and Drug Administration's efforts in this direction it will be necessary to summarize its basic trends toward such a goal.

The Food and Drug Administration is a result of the desires of the American people through Congress to have a more effective and informed regulation of the foods, drugs, and cosmetics which they use. The FDA has evolved to its present state as the result of over 57 years of legislative action. There was and is a realization that, however effective and informed the regulatory personnel within the FDA structure were, the ultimate regulation by the FDA of the rapidly developing pharmaceutical industry necessitated a profound appreciation by

* Presented at a meeting of the Section on Obstetrics and Gynecology of The New York Academy of Medicine, January 28, 1964.

it of the biological sciences, an intimate association with pharmacologists and their societies, and a research staff of its own to probe into those problems which it alone could adequately study and for which it alone was equipped. It has thus in 1964 become a regulatory agency inextricably woven into the fabric of critical scientific analysis. Its facilities have by the very force of the developing logic within the field of clinical pharmacology been extended to cope with its unique position in this discipline.

Viewed in this perspective then, the thalidomide episode and the related Kefauver-Harris Amendments which I shall soon discuss provide the basis for the expanded responsibility now assumed by the staff of the FDA. This necessarily includes protecting the American public from drugs which might be injurious to the developing fetus.

Among the problems with which the FDA must daily contend is the fact that we are entrusted with the role of preventing any possible occurrence, at least here in the United States, of a thalidomide-type episode. Let us examine then, in some depth, what in fact is the meaning of the recent legislation insofar as the preceding remarks may be concerned.

Although the problem of safety of drugs in pregnancy has been receiving great attention recently, this matter was of great concern to the Food and Drug Administration prior to the thalidomide episode. Special attention was given to drugs taken by the mother during late pregnancy or given to the child shortly after birth. Many enzyme systems may in fact not be fully developed in the infant, and therefore the baby in such cases may be more susceptible to certain drugs than the adult.

It was also recognized by the Food and Drug Administration that a number of drugs did have a teratogenic effect. Such drugs included certain steroids with masculinizing effects on the female fetus and certain antineoplastic drugs such as the folic acid antagonists. What the thalidomide episode did in effect was to dramatize the possibility that other drugs might exert similar effects and raise the question as to how such an activity could best be detected both experimentally and clinically.

It is not sufficient to assume that a given drug, merely because of its long history of administration to women in the child-bearing age, is *not* capable of producing damage to the developing fetus at any stage

from fertilization, through implantation, to organogenesis. Drugs affecting the fertilized ovum in the early stages of cell division have been under consideration by the FDA. Medical knowledge of the action of certain drugs, even at this early stage, is still too meager to warrant complacency.

Certainly we cannot be satisfied by a report that this or that animal has no gross skeletal deformities. Abnormalities such as cleft palate, cleavage of the tongue to the roof of the mouth, and decalcification of the neural arch have eluded even the skilled investigator. Quite apart from this are the elusive problems of implantation difficulties and fetal resorption, not to mention genetic defects imparted to the developing and fertilized germ cell by an abnormal ovum.

Fetal death, stillbirth, and nonsurvival of the young may give some indication of fetal toxicity. This was observed in the tests with thalidomide. Failure of pregnancy, resorptions, and stillbirths occurred in most species up to the monkey, while only certain rabbits, mice, and rats exhibited malformations on persistent experimentation. Fetal deaths generally mean that the drug is toxic to the fetus and is an abortifacient. Under specific conditions of administration there may be a likelihood of malformation. The multiplicity of factors in treatment of a pregnant woman is under study by the FDA and the National Institutes of Health.

The FDA recommends that screening tests be done in animals before a drug is used in women of the child-bearing age. As a minimal requirement, we suggest a litter test in rats which consists essentially of feeding subtoxic doses to male and female rats for a preliminary period of six weeks and then through two pregnancies. This test is intended to detect drugs which affect spermatogenesis, fertilization or implantation, which cause teratogenic effects or otherwise adversely affect the rat fetus or the welfare of the newborn.

Responsible investigators recognize that other tests yet to be developed may and probably will be better. This is the best we have now, and in the case of thalidomide, a number of investigators have shown that when the drug is administered to rats before pregnancy and continued through early pregnancy, there is a significant reduction in litter size due to resorption of the embryos. Thus, the litter test would have alerted investigators to the possibility of an ill effect of this drug in pregnancy.

There is the question of what significance should be attached to positive teratogenic effects in animals. This question is an admittedly difficult one to answer. However, if ill effects are seen, certainly such factors as absorption and blood levels of the drug and its metabolic patterns in various species should be more closely examined. Furthermore, if a drug showing teratogenic effects in one or more species of animal is used during human pregnancy, very close records should be made including the exact dosage, period of administration of the drug and clinical follow-up.

All too often reports dealing with drugs taken during pregnancy are poorly documented in this respect. It is necessary, for example, to have more accurate information than simply that the drug was taken during the first trimester since it is apparently well established that the ill effects from thalidomide occur primarily between the 27th and 40th day of pregnancy. Furthermore, since not all congenital defects are recognized at birth, adequate follow-up studies of the baby are necessary. In fact, the NIH Perinatal Study group expects to include a seven-year follow-up period.

Finally, negative animal findings alone do not establish the assumption that the drug is safe for use in pregnant women. Once again careful clinical studies should be done to attempt to establish this point and, pending the outcome of such studies, the indiscriminate use of the drug during pregnancy should be avoided. Establishing the safety of drugs during pregnancy is no easy task particularly since some recognizable congenital deformity is said to be present in approximately 5 per cent of all newborn infants. If such is the case, then to establish at the 95 per cent confidence level that a given drug changes the incidence by 1 per cent would require a sequential trial involving 35,500 patients. To show differences of 10 and 20 per cent would require sample sizes of 560 and 180 respectively.*

Objectively designed clinical studies with thalidomide should have detected both the neuropathy and embryopathy long before those side effects caused such widespread damage. The clinical studies submitted in support of the application for thalidomide in this country did not record either side effect. Retrospective inquiries, however, disclosed several cases of both neuropathy and phocomelia that had not been re-

* Weiss, W. Effects of Drugs on the Outcome of Pregnancy: Conference on Research Methodology and Needs in Perinatal Studies, University of North Carolina, September 9-11, 1963.

ported, the investigators having considered the effects to be unrelated to the drug under test.

It is known that one single dose of 100 mg. of thalidomide to the mother may induce phocomelia in the fetus. Yet there is no apparent relationship between the amount of the drug ingested and the severity of the malformation. Difficulties inherent in good prospective and good retrospective studies thus become apparent. If a mother has been taking many drugs during the period of her pregnancy it will be difficult to establish any causal relationship between the development of a malformed embryo and a specific drug. It becomes of greatest importance that doctors administering drugs to women during the period of pregnancy prescribe only those drugs which are absolutely necessary for the safety and health of the mother and the fetus. As Doctor Dale Friend has recently stated, "the wise physician will, therefore, prescribe these drugs for pregnant women only when sound indications exist, and discontinue their use as quickly as the situation allows." It is obvious also that it is imperative that pregnancy be recognized as early as possible.

Thalidomide is estimated to have caused a teratogenic effect in some 20 per cent of cases in which the mother took the drug during the critical period, but unfortunately no controlled studies preceded its introduction on the market or were undertaken after its release, despite the fact that in some countries at least it was distributed for use in nausea of early pregnancy. Assuming the "normal" incidence of recognizable birth defects to be approximately 5 per cent, an increase to 20 per cent could be detected with a reasonable degree of significance by exposing fewer than 100 pregnant women to the drug.

The minimum reproduction study which the Food and Drug Administration is now suggesting consists of one or two test groups and one control group of 20 male and 20 female rats each, followed through two litters. The test rats, both males and females, should be dosed with the drug (at dose levels just below those showing toxicity in other repeated dose studies) for at least 60 days before the first mating, and dosing should continue through weaning of the second litter (or third litter if necessary). The first litter is to be sacrificed at the weaning time and the mating pairs rerandomized before breeding for the second litter. A third litter would be necessary only if the results from the first two were inconsistent. Observations on the offspring in addition

to teratogenic effects would include number born, survival, and growth rates, which also indirectly give fertility and lactation data on the parent stock. In addition, this provides some information on the toxicity of the drug in immature animals in that the newborn animals would get any drugs excreted in the milk and would be receiving drug in their food.

The Food and Drug Administration feels that the reproduction test outlined above gives the most information regarding the injury to the fetus or difficulties in implantation. It is admittedly a crude method. The only other animal feasible for this type of test is the rabbit. However, the rabbit is a capricious animal with numerous strain differences. We are aware that a number of other countries which have a Food and Drug Administration have established testing procedures asking that at least two species of animals be used in the reproduction tests.

If this reproduction test discloses positive evidence of abnormal reproduction, the Food and Drug Administration may then notify the firm to desist from human testing in the child-bearing age until further tests are performed. In a number of cases firms with positive tests of this type do not choose to pursue further experimental work. In other cases there may be a question of dosage effect on the host animal or a question of pharmacological change of the drug in the animal itself.

There have been drugs in the investigational phase which acted as an abortifacient during the middle period of pregnancy. In some instances the drug companies have chosen to withdraw the drug from further experimentation. In other cases cataracts in the fetus have been found during the period of drug administration to the mother and the investigation has been voluntarily stopped.

Injection of a drug into the yolk sac of the developing chick embryo offers a promising and convenient method for the screening of drugs for a possible teratogenic effect. In the Division of Pharmacology at the Food and Drug Administration extensive testing has been performed with the use of the chick embryo over the past several years. It is hoped that new leads into a predictable test for human teratogenicity will be developed.

Studies are planned and under way to use pigs for eliciting reproductive effects of drugs. This is under the supervision of our Division of Pharmacology at Beltsville, Maryland. However, this again is another instance of a species which may or may not have a direct appli-

cation to man. Other members of our Division of Pharmacology plan to study the effect of drugs on the reproduction of the hamster, which has a short gestation period and has fewer problems with the estrus cycle than does the rat. There is a plan to study certain steroid groups on several species of rats.

The recognition and utilization for pharmacological testing of strains of animals with hereditary defects or other special characteristics is a relatively unexplored field of great potential value. A new branch of science called *pharmacogenetics* has developed in recent years indicating the close contact between geneticists and pharmacologists. Our staff at the Food and Drug Administration is acutely aware of this and is following every lead as closely as possible.

At this point it may be well to review briefly some provisions of the Kefauver-Harris Drug Amendments of 1962. Fundamentally there were two objectives advanced by these amendments. First, the new legislation was designed to assure both the safety and effectiveness of drugs. Second, it was designed to improve the communication of necessary information concerning these drugs, their side effects and contraindications, as well as their advantages. Specifically these two related objectives are advanced by provisions which require: 1) substantial evidence of the effectiveness of new drugs before marketing; 2) all drugs to be manufactured under adequate control and "good manufacturing practices"; 3) government certification of both the safety and effectiveness of all antibiotics for human use; 4) prompt reporting by manufacturers to the government of adverse reactions attributed to new drugs and antibiotics; 5) truthful statements in prescription drug advertisements concerning the effectiveness, side effects, and contraindications of the advertised drugs; 6) annual registration with the Food and Drug Administration of all persons and firms engaged in the manufacturing, repacking, and relabeling of drug products; and 7) inspection of every registered establishment at least once every two years. The new law further authorizes the Food and Drug Administration: 1) to establish official names for drugs in the interest of usefulness and simplicity; 2) to withdraw approval of drugs when substantial doubt arises as to their safety or in the absence of substantial evidence of effectiveness; 3) to have access during inspection of prescription drug manufacturing establishments to all things which have a bearing on violations of the law with respect to such drugs,

including records, files, papers, processes, controls, and facilities; and 4) to exercise greater controls over shipments of investigational drugs for testing in man. The improved controls over investigational drugs deserve particular mention. The new law and regulations require that before a new drug may be shipped interstate for clinical investigation, the sponsor must be sure that tests on man are justified. Among other things he does this by: 1) determining that adequate preclinical tests have been made on animals and in the test tube; 2) developing an adequate plan of investigation; 3) obtaining competent investigators to test the product; and 4) making an appropriate report to the government before the drug is shipped for administration to humans.

These controls are a desirable safeguard for patients; they also offer protection to those engaged in medical research by the full disclosure that adequate preclinical studies have been made as a prelude to the clinical investigation of new drugs. To place greater emphasis on its scientific activities the Food and Drug Administration has recently undergone a reorganization. The effects of this reorganization on the ultimate scientific responsibilities and evaluation of drugs assumed by the FDA will be felt with a passage of time. The following high-level changes have been made: 1) A new Associate Commissioner who will be a scientist will provide leadership from the Office of the Commissioner to the scientific and enforcement bureaus concerning medicine, science, and research. He will be directly responsible to the Commissioner. 2) A National Advisory Council will be formed, comprised of representatives of industry, universities, government, consumers, and other groups. It will advise the Food and Drug Administration on national needs and the effectiveness of program policy. It will also be responsible to the Commissioner. 3) Two new bureaus with scientific responsibilities have been established. They are the Bureau of Scientific Research, and the Bureau of Scientific Standards and Evaluation. It thus becomes apparent that both through the Commissioner's office and the various scientific Bureaus extensive personnel changes are taking place which will permit the detailed analysis, correlation, and evaluation of data both within and without the Food and Drug Administration on a much more effective basis than was hitherto possible.

The staff in the Bureau of Medicine has been expanded and all medical officers are keenly interested in the potentials of drug-induced fetal damage. Our obstetricians and pediatricians have begun an ex-

tensive survey of all drugs which have been reported to be associated with fetal damage, all classes of drugs which might be associated with fetal damage, and all analogues of drugs which have had some association with fetal damage. They constantly consult outside experts and, when necessary, committees will be formed to advise the Bureau.

To cope effectively with its increased responsibilities under the Kefauver-Harris Amendments and to keep abreast of rapidly changing developments, the Division of New Drugs of the Bureau of Medicine has been reorganized, and now consists of five branches. They are: 1) The New Drug Status Branch, whose functions will be to consult with manufacturers and others with respect to the new drug status of chemicals newly proposed for drug use and to new uses or dosage schedules for drugs already on the market. 2) The Investigational Drug Branch, which will review the information submitted by the sponsor of a new drug pertaining to its use in investigational studies. 3) The Medical Evaluation Branch, consisting of medical officers who will evaluate the medical safety and efficacy data in new drug applications. 4) The Controls Evaluation Branch, whose chemists will evaluate the adequacy of laboratory and manufacturing controls proposed by manufacturers of new drugs. 5) The New Drug Surveillance Branch, which will be concerned with following experience with new drugs after applications are approved.

The Food and Drug Administration has increasingly been associated with programs on teratogenicity. Members of the staff of the Bureau of Medicine have participated in numerous committees and panel discussions on this problem. They have discussed every phase of this subject with pediatricians, obstetricians, and pharmacologists throughout the United States. Foreign pharmacologists frequently visit the Food and Drug Administration and give members of its staff an intimate acquaintance with the nature of their work and, in many cases, the FDA staff is afforded the privilege of reviewing basic unpublished work which pertains to this particular problem. The FDA encourages participation of its staff in the work of medical societies and is willing and happy to associate itself in any proper way with the developing of programs on fetal drug toxicity by the various societies representing the medical disciplines.

How can the FDA deal with the problem of labeling those drugs which might be injurious to the fetus? When there is sound basis to

suspect that a drug may cause human fetal abnormalities we can require it to be dispensed only on prescription and can require appropriate warnings such as against its use in women of child-bearing age. Even if the drug is contraindicated in pregnancy, there might still be a use for it in certain selected cases. For instance, such a drug might be employed for chronic diseases of the elderly, or in humans experimentally as a research tool, as for example in certain specific cases of diabetes, where there may be a question of insulin allergy and an oral antidiabetic might be indicated.

How can the FDA keep itself informed of all experience with an approved new drug? Recent amendments to the Food, Drug, and Cosmetic Act, together with the new regulations relating to these amendments, provide that an applicant, whose application for a new drug has been approved, must maintain information covering clinical and animal experience, studies, investigations and tests conducted by or reported to him, together with reports in the scientific literature related to the drug; experience, investigation, studies, or tests on the chemical, physical, "or any other properties of the drug"; copies of all mailing pieces and other labeling, and if it is a prescription drug, all advertising used in promoting the drug. The applicant, if a drug is to be administered to man, must submit the above information to the FDA at intervals of three months after the date of approval during the first year, at intervals of six months during the second year, and at yearly intervals thereafter.

The applicant must submit to the Food and Drug Administration, at least *within 15 days* of his receipt, complete records or reports concerning information obtained on any "unexpected side effect, injury, toxicity, or sensitivity reaction" encountered, or any information concerning any unusual failure of the drug to exhibit its expected pharmacological activity. Daily contact from Washington is maintained with the 18 district offices of the Food and Drug Administration. Through the Bureau of Medicine's newly established New Drug Surveillance Branch immediate contact with the district offices can be made to follow up any individual case report and to obtain all data concerning that case report by a District Inspector on the scene.

What else is the FDA doing to become more constantly and immediately informed of the danger of drugs to the fetus?

1) There is a continuous surveillance of the key world literature

and of all case reports submitted by the district offices of the Food and Drug Administration located throughout the United States. Reports of adverse drug reactions are also submitted by approximately 450 hospitals and related institutions; the number of hospitals reporting is being increased.

2) The Kefauver-Harris Amendments and the Investigational New Drug regulations require the sponsor of a clinical test to exercise proper care—which in extreme cases may mean abandoning the trials when the evidence indicates that there may be injury to the fetus.
3) The use by the Food and Drug Administration of ad hoc committees and expert standing committees to deal with specific problems of drugs, including the problem of use of drugs during pregnancy, is now being actively enlarged in scope.
4) The FDA has been in close contact with the National Institutes of Health's Perinatal Study since its inception. The FDA has been consulted by the NIH on those questions with which the FDA will be most involved. In this manner, it is hoped that the proposed NIH prospective study to which I have previously referred will be most informative.

The success of the programs which are currently in use for reporting drug reactions depends for the most part on the ability of the individual physician to recognize drug reactions and his willingness to report these to a coordinating agency where they can be evaluated in a fair, confidential, and impartial manner and appropriate measures taken. An additional safeguard would be the establishment of a national or international adverse reaction program based on a register of medical case histories which would permit an independent observer to detect correlations between drug intake and toxicity that might elude the individual clinical investigator or attending physician.

Largely as the result of the impetus provided by the thalidomide episode the World Health Organization has initiated a campaign aimed at providing a drug-warning system throughout the world. Resolutions were passed which will enable countries to obtain information on adverse reactions to drugs anywhere in the world. These resolutions were passed in May of 1963, at the 16th Annual World Health Assembly. This program is actively supported by the FDA, and the speaker has been afforded the unusual opportunity of representing the

FDA and attending the initial meetings in Geneva, Switzerland, where resolutions to institute this important data collection were proposed. The Food and Drug Administration was of aid in establishing an atmosphere of immediate urgency for this need. Two resolutions were passed which establish a department of clinical pharmacology in the World Health Organization. This organization will be extended. Already the Food and Drug Administration is sending to and receiving from the World Health Organization reports on adverse effects of drugs. We feel that this is an extremely important first step toward an international drug safeguard plan.

With such an all-encompassing program in action it should not take many thousands of deformed children to establish the degree of hazard that is associated with a thalidomide-like drug. It would certainly add to the tragedy of the thalidomide episode if we did not accept the fact that this could largely have been averted and act accordingly both nationally and internationally.

Close liaison is being established with specific European centers of pharmacology, with the European pharmaceutical industries, and with key European clinicians concerned with the problem of adverse reaction to drugs and especially drug-associated teratogenicity. This is being done directly on a bilateral basis, through the scientific attachés of the State Department. Contacts have been made between the FDA and both the European Free Trade Association and the European Economic Community. The Food and Drug Administration is taking a vital interest in all these organizations and sincerely hopes that such international cooperation will help in preventing another thalidomide disaster.

The Food and Drug Administration is in continuous contact with the European Society for the Study of Drug Toxicity. This recently formed organization embraces most of the pharmaceutical manufacturers in Europe. It has recently initiated several studies on the effects of drugs on the fetus. This is a collaborative approach by manufacturers intended primarily to develop new methods in the evaluation of fetal toxicity. Reproducibility of results in different laboratories will be evaluated in a forthcoming study. We at the FDA are keeping close contact with this group, and hope that it will come forth with a serious and significant approach to this subject. We are keeping in close touch with the American Medical Association's plans to expand its drug reaction reporting program to include all drug reactions rather

than just those associated with blood dyscrasias as in the past.

Additionally, the 1962 Kefauver-Harris Amendments require that pharmaceutical firms report at regular intervals to the FDA all adverse reactions associated with their approved new drugs. The success, of course, of any reporting program depends on the ability of any individual physician to recognize a drug reaction, to report it to a central coordinating agency, and to have it evaluated by such an agency in a fair and impartial manner so that appropriate precautions may be taken.

Rapid retrieval of information is essential in order to correlate the large masses of data present in the files of the Food and Drug Administration. This may be of importance in evaluating data on chemical structures which may be associated with production of abnormalities in the fetus. For this purpose, Project Rapid (retrieval and automatic processing of information on drugs) was established in the Bureau of Medicine in June of 1963. This is a data-retrieval operation designed to help relieve the already existing burden of scientific information needs in the Bureau of Medicine as well as to correlate data with that obtained from other areas of the FDA and elsewhere. The system supplies the medical officers and pharmacologists with early information on such things as chemical structure, generic name, pharmacological activity, route of administration, dosage form, therapeutic indication, manufacturer's name and pertinent administrative data, and trade name. These data are then utilized in review of data in investigational or new drug applications, in the experiments performed in our Division of Pharmacology, and in other ways.

A number of drug manufacturers are retesting their products for use during pregnancy. These include producers of antihistamines, analgesics, tranquilizers, diuretics, and hypoglycemic agents. Many manufacturers have voluntarily decided to retest and reevaluate their drugs during reproductive periods in animals and to restudy the clinical and experimental data as well as the literature on the subject.

I have attempted to delineate in some detail the many-faceted approaches being followed by the FDA in its quest to give the woman of child-bearing age some degree of security when taking drugs. Certainly there remain avenues unknown to us today which will become evident and feasible tomorrow. But we know that we are not sparing any effort or overlooking any lead, anywhere in the world, which might bring us closer to the answer.